HFA-305
(Dockets)

SEP 29 2000

FREEDOM OF INFORMATION SUMMARY

Original New Animal Drug Application

NADA 141-176

BAYTRIL® ® OTIC

(enrofloxacin/silver sulfadiazine)

Antibacterial-Antimycotic Emulsion

For Ototopical Use in Dogs

Sponsored by:

Bayer Corporation
Agriculture Division
Animal Health

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I. GENERAL INFORMATION

NADA Number: 141-176

Sponsor: BAYER Corporation,
Agriculture Division,
PO Box 390
Shawnee Mission, Kansas 66201-0390

Accepted Name: enrofloxacin/silver sulfadiazine

Trade Name: Baytril® Otic

Marketing Status: A prescription (Rx) product which carries the following caution statement: "Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian."

II. INDICATIONS FOR USE

Baytril® Otic is indicated for the treatment of canine otitis externa complicated by bacterial and fungal organisms susceptible to enrofloxacin and/or silver sulfadiazine.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND DOSAGE

Dosage Form: Baytril® Otic is available in 15 mL and 30 mL oval plastic bottles with a dropper tip and extended tip enclosure. Each mL contains 5 mg enrofloxacin and 10 mg silver sulfadiazine.

Route of Administration: Baytril® Otic is topically applied to the ear canal.

Recommended Dosage:

Shake well before each use.

Tilt head so that the affected ear is presented in an upward orientation. Administer a sufficient quantity of Baytril® Otic to coat the aural lesions and the external auditory canal. As a general guide, administer 5-10 drops per treatment in dogs weighing 35 lbs. or less, and 10-15 drops per treatment in dogs weighing more than 35 lbs. Following treatment, gently massage the ear so as to ensure complete and uniform distribution of the medication throughout the external ear canal. Apply twice daily for a duration of up to 14 days.

IV. EFFECTIVENESS

A. Dosage Characterization

1. *In vivo* Enrofloxacin Titration

a. **Type of Study / Purpose:** This controlled, double blind, *in vivo* study was undertaken to identify the appropriate ototopical concentration of enrofloxacin for the treatment of experimentally–induced canine otitis externa.

b. **Investigators:**

Michael Groh DVM
H. Dennis McCurdy DVM
Daniel K. Ciszewski DVM
Bayer Corporation
DeSoto Animal Research Facility
35040 W. 87th Street
DeSoto, KS 66018

c. **General Design:**

1. Animals: Adult, male (n=6) and female (n=14), crossbred dogs with dependent pinnae

2. Treatments: Treatments included 3 different enrofloxacin concentrations (0.1%, 0.3%, 0.5%) and a negative control (placebo). All treatments were packaged in opaque 10-mL dropper-tip bottles that were identified by coded laboratory labels. Study investigators were blinded to the identities of the treatments.

3. Treatment Group Assignment / Randomization: A computer-generated randomization schedule was used to assign dogs to treatment groups.

4. Experimental Infection: The epithelium of the external auditory meatus was mechanically and chemically irritated and a culture of *Pseudomonas aeruginosa,* with low enrofloxacin susceptibility (MIC = 16), was instilled into the canal.

5. Treatment Dose, Route, Frequency and Duration: A standardized volume of 0.5 mL (~10 drops) per treatment, was selected. Treatments were administered ototopically, 2X daily, for 14 consecutive days.

6. Clinical Examination / Clinical Scoring: Challenged ears were examined otoscopically and scored at pretreatment, mid-treatment, late-treatment, final treatment and 3-4 days post-treatment. During each examination, ears were examined for the characteristic clinical signs of otitis externa (erythema, swelling, exudate, ulceration/erosion, malodor and pain) and a composite clinical score, based on severity (range: 0 to 12), was assigned. A score of at least 6 was required to qualify for entry into the study. Otoscopy and clinical scoring were consistently performed by the same blinded investigator.

d. **Results:** A post-treatment score of ≤ 2, or 3 – 4 and a negative culture, were required to qualify as a treatment success. The results are shown in Table IV.1.

Table IV.1: Clinical Score (Group Avg.) & Treatment Success, by Treatment & Day

Treatment	n	Pre-treat	Mid-treat	Late-treat	Final treat	Post-treat
0.1% Enrofloxacin		8.4	5.4	5.3	4.0	3.3
	12	NA	17% (2/12)	25% (3/12)	42% (5/12)	50% (6/12)
0.3% Enrofloxacin		8.3	5.6	4.6	3.1	2.7
	12	NA	8% (1/12)	25% (3/12)	58% (7/12)	75% (9/12)
0.5% Enrofloxacin		8.8	4.2	4.6	2.7	2.2
	12	NA	25% (3/12)	33% (4/12)	50% (6/12)	83% (10/12)
		8.5	6.5	5.2	4.5	3.5
Placebo	11	NA	0% (0/11)	9% (1/11)	27% (3/11)	55% (6/11)

e. **Conclusion:** The results support 0.5% as an appropriate enrofloxacin concentration for the topical treatment of experimentally induced canine otitis externa.

2. *In Vitro* Susceptibility Study

a. **Type of Study:** This study was conducted to determine the *in vitro* susceptibility of select organisms to enrofloxacin and to silver sulfadiazine (SSD).

b. **Investigator:**

John N. Berg, DVM, PhD
Department of Veterinary Microbiology
104 Connaway Hall
University of Missouri
Columbia, MO 65211

c. **General Design:**

1. Objectives: The study had 2 objectives.

   (1) to determine the minimum inhibitory concentrations (MIC) of enrofloxacin and SSD to canine aural bacterial and fungal organisms, and

   (2) to identify the minimal *in vitro* concentration of each anti-infective required to ensure broad antimicrobial activity against all organisms studied.

2. Samples: A total of 72 microbial isolates, originating from clinical cases of canine otitis externa, were evaluated.

3. Procedure: An agar dilution method, described by the National Committee for Clinical Laboratory Standards [" Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically" (Vol. 10, No 8, 1990)], was used to determine the Minimal Inhibitory Concentrations (MICs). Serial twofold dilutions of enrofloxacin and SSD, in concentrations from 0.004 – 32 and 3.125 – 500 micrograms per mL, respectively, were used to determine the *in vitro* susceptibility of the microbial organisms.

4. Test Duration: January to May, 1993

5. Measured Variables: Enrofloxacin and SSD MIC ranges were determined and recorded for the 72 isolates. Whenever possible, MIC50 and MIC90 were also reported.

d. **Results:** The results are shown in Table IV.2.

Table IV.2 Minimum Inhibitory Concentrations (mcg/mL) for Enrofloxacin and Silver Sulfadiazine

Organism / Antimicrobial	n	MIC Range (mcg/mL)	MIC_{50*}	MIC_{90*}
GRAM POSITIVE				
Staphylococci spp (coagulase +)	13			
Enrofloxacin		0.06 – 0.125	0.125	0.125
SSD		25 - 200	25	25
Streptococci spp (β-hemolytic)	9			
Enrofloxacin		0.5 – 1.0	**	**
SSD		50 -100	**	**
GRAM NEGATIVE				
P. aeruginosa	15			
Enrofloxacin		1 – 16	1.0	16.0
SSD		12.5 - 50	25.0	25.0
Escherichia coli	7			
Enrofloxacin		0.03 – 0.062	**	**
SSD		25.0	**	**
Proteus spp	7			
Enrofloxacin		0.125 – 0.5	**	**
SSD		25.0	**	**

Organism / Antimicrobial	n	MIC Range (mcg/mL)	MIC_{50*}	MIC_{90*}
Klebsiella. Pneumoniae	5			
Enrofloxacin		0.06 – 0.125	**	**
SSD		6.25 - 25	**	**
YEAST / FUNGI				
Malassezia spp	12			
Enrofloxacin		> 32	> 32	> 32
SSD		100	100	100
Candida spp	4			
Enrofloxacin		> 32	**	**
SSD		25.0 - 300	**	**

* MIC50 - The minimum inhibitory concentration for 50% of the isolates.
MIC90 - The minimum inhibitory concentration for 90% of the isolates.
**There were an insufficient number of isolates to calculate the MIC_{50} and MIC_{90}.

e. **Conclusions:**

Enrofloxacin did not inhibit *in vitro* growth of *Malassezia* or *Candida* spp. at concentrations up to 32 mcg/mL.

Enrofloxacin exhibited its lowest *in vitro* activity against the bacteria *Pseudomonas aeruginosa* (MIC90 = 16.0 mcg/mL).

SSD exhibited its lowest *in vitro* activity against the fungi *Candida* spp (upper limit of MIC range = 300 mcg/mL).

Therefore, to be clinically effective for mixed infections, an enrofloxacin and SSD combination product should be able to deliver sufficient *in vivo* concentrations of each active ingredient (enrofloxacin, >16.0 mcg/mL and SSD, >300.0 mcg/mL) to eliminate these organisms while under the complicated conditions associated with active disease. The concentrations of the two drugs in the final market formulation of Baytril® Otic exceed these amounts.

B. Drug Interactions Associated with the Combination of Enrofloxacin and Silver Sulfadiazine

1. **Type of Study:** This *in vitro* study was conducted to characterize the types of interactions occurring between enrofloxacin and silver sulfadiazine (SSD) in the presence of assorted canine aural microbial organisms.

2. Investigator:

John N. Berg DVM, PhD
Department of Veterinary Microbiology
104 Connaway Hall
University of Missouri
Columbia, MO 65211

3. General Design

a. Objectives: The objectives of this laboratory study were: (1) to calculate fractional inhibitory concentration indices (FICI) for strategic enrofloxacin/SSD combinations (combinations in which the enrofloxacin: SSD concentration ratios equal the ratios of their MICs), (2) to classify each FICI into the appropriate interactive category: synergistic, additive, indifferent or antagonistic, and (3) to demonstrate, in accordance with 21CFR 514.1(b)(8)(v), that each drug makes a contribution to the antimicrobial effect.

b. Samples: Minimum Inhibitory Concentrations (MICs) to enrofloxacin and SSD were determined for 72 microbial isolates cultured from clinical cases of canine otitis externa. Sixty-five of these isolates, and their corresponding MICs, were used to determine FICIs.

c. Procedures: An agar dilution method, described by the National Committee for Clinical Laboratory Standards ["Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically" (Vol. 10, No 8, 1990)], was used to determine the 90% Minimal Inhibitory Concentrations (MIC90).

FICIs were calculated with results obtained from a standard checkerboard evaluation of the antimicrobial combination versus the 65 aforementioned microbial isolates. Concentrations of antimicrobial combinations used in test wells were determined by MIC results and included levels at approximately 3 dilutions above and 3 dilutions below the MIC. The experimental procedures used for this portion of the study are similar to those described by Eliopoulos and Moellering (Antimicrobial combinations. In: Lorian V, editor. Antibiotics in Laboratory Medicine, edition 4, Baltimore: Williams & Wilkins, 1996; 330-396).

d. Test Duration: January to May 1993

e. Measured Variables:

(1) FICIs were calculated as follows:

$$(X)/(MICX) + (Y)/(MICY) = FICX + FICY = FICI$$

Where (X) is the enrofloxacin concentration that is the lowest inhibitory concentration in its row, (MICX) is the MIC of the microbe to enrofloxacin alone and FICX is the fractional inhibitory concentration of enrofloxacin. (Y), (MICY) and FICY are defined similarly but apply to SSD.

(2) The types of antimicrobial interactions are defined by the following FICI values:

FICI < 0.5 = synergism

FICI ≥ 0.5 but ≤ 2.0 = additivity to indifference/autonomy

FICI > 2.0 = antagonism

f. Results: Table IV.3 summarizes the results of the *in vitro* interactions between enrofloxacin and SSD.

TABLE IV.3: *In vitro* Interactions between Enrofloxacin and Silver Sulfadiazine

Organism	Number of Isolates	Enrofloxacin MIC (mcg/mL)	SSD MIC (mcg/mL)	FICI*
P. aeruginosa	5	1	50	0.625
	5	2	50	0.562 / 0.562**
	1	16	50	0.507
	1	16	25	0.750
	1	8	50	0.562 / 0.515**
	1	2	50	0.562 / 0.625**
	1	1	50	0.562 / 0.625**
Staphylococci sp. (coagulase +)	4	0.0625	25	1.500
	4	0.125	25	1.500
	4	0.125	25	1.500
Streptococci sp. (β-hemolytic)	2	0.5	12.5	1.500
	4	0.5	12.5	0.750 / 0.750**
	1	1.0	12.5	0.750
	1	0.5	25	0.625 / 0.750**
Malassezia sp.	11	> 64	100	1.500
Escherichia coli	3	0.031	25	1.500
	1	0.031	25	0.600
	2	≤ 0.0625	25	0.360

Table IV.3 continued

Organism	Number of Isolates	Enrofloxacin MIC (mcg/mL)	SSD MIC (mcg/mL)	FICI*
Proteus sp.	1	0.5	50	4.060 / 2.500**
	1	0.125	50	2.060 / 0.620**
	1	0.125	50	2.060 / 0.620**
	1	0.25	50	2.060 / 1.250**
	1	0.25	50	1.500
	1	0.50	50	2.060 / 1.500**
	1	0.25	50	0.560
K. pneumoniae	2	0.125	50	0.620
	1	0.125	25	1.500
	1	0.0625	50	0.740
Candida sp.	1	> 64	200	1.500
	1	> 64	400	1.750

* FICI - Fractional inhibitory concentration index
**Indicates results from a repeat *in vitro* evaluation

Table IV.2 lists 41 Fractional Inhibitory Concentrations. Unequivocal evidence, supporting either antagonism or synergy, can only be found in 1 *Proteus* and 1 *E. coli* comparison (2 of 41 or 4.9% of the overall total), respectively. Most of the critical FICIs (34 of 41 or 83% of the total) were between 0.5 and 2.0, and as such, were indicative of either additivity or indifference. Furthermore, of these 34 FICIs, 22 (54% of the total) closely approached the 0.5 value (FICI < 1), and therefore, were more consistent with additivity rather than indifference.

g. Conclusions:

Results of *in vitro* tests to determine FICIs demonstrated a lack of interference between the 2 active ingredients. Minimal inhibitory concentrations indicate that enrofloxacin is a potent antibacterial with marked efficacy against gram negative bacteria (i.e. *Pseudomonas aeruginosa*) and that SSD, while possessing some antibacterial activity (including gram positive bacteria, i.e. *Streptococci* sp.), is uniquely active against yeast and fungi. Therefore, to ensure consistent effectiveness against the range of microorganisms (gram negative and gram positive bacteria, yeast and fungi) commonly associated with canine otitis externa, both active ingredients are essential.

C. Clinical Field Study

1. **Type of Study:** This was a controlled, double blind, multi-site, clinical effectiveness and safety study. It was conducted at 7 veterinary hospitals. A total of 169 dogs participated in the trial.

2. **Investigators:**

Craig Staehle, DVM / Lisa Shopmyer, LVT
Sunshine Animal Hospital
8008 W. Waters Ave.
Tampa, FL 33615

Michael Ferguson, DVM / Beth Reinhardt, LVT
Rock Hill Animal Hospital
549 S. Cherry Rd.
Rock Hill, SC 29732

Richard Heers, DVM / Krissi Mederos / Sherry O'Neal
Cross Street Veterinary Clinic
400 E. Cross St.
Tulare, CA 93274

John Kelley, DVM / Jennifer Quenneville, LVT
Eastham Veterinary Hospital
725 State Highway
Eastham, MA 02642

Ted Lamp, DVM / James Lamp, DVM
Bellville Veterinary Hospital
957 E. Hill St.
Bellville, TX 77418

Richard Mauldin, DVM / Roul Jaques
Hillcrest Animal Hospital
5720 S. Penn
Oklahoma City, OK 73119

Jan Strother, DVM / Elaine Moore, DVM
N. Alabama Cat & Bird Clinic
809 Hwy 36 E
Hartselle, AL 35640

3. **General Design:**

a. Purpose: The clinical trial was conducted to evaluate the effectiveness and safety of Baytril® Otic, when used according to label directions under field conditions, as a treatment for the bacterial and/or fungal infections that accompany and complicate both acute and chronic canine otitis externa.

b. Animals: One hundred and sixty-nine dogs qualified for study enrollment. Gender distribution included 19 intact females (11%), 59 neutered females (35%), 41 intact males (24%) and 50 neutered males (30%). Patient ages ranged from 4 months to 15 years. Forty-one different breeds were represented with the predominant breeds being Mixed (29/17%), Labrador Retriever (24/14%), Cocker Spaniel (21/12%), Poodle (13/8%), Golden Retriever (13/8%) and Shih Tzu (7/4%).

c. Enrollment Criteria: Ears were examined for the characteristic clinical signs of otitis externa (erythema, swelling, exudate, ulceration/erosion, malodor and pain) and a composite clinical score, based on severity (range: 0 to 12), was assigned. To qualify for study inclusion, a clinical score ≥ 6 was required.

d. Exclusion Criteria: Recent systemic antimicrobial and/or anti-inflammatory therapy, ruptured tympanic membrane, concurrent infections with *Otodectes cynotis,* poor general health or poor anesthetic risk were reasons for exclusion.

e. Treatment Groups and Controls: Animals were assigned to 1 of 3 treatment groups. The appearance, physical characteristics, packaging and labeling of the 3 treatments were identical. Treatments A and C contained active ingredients and were identical in formulation to the product intended for market. Except for the absence of active ingredients, Treatment B (placebo) contained all other formulary components (negative control). Throughout the study, the identity of the experimental treatment remained unknown to both investigators and clients. By study conclusion, 113 (67%) and 56 (33%) cases had been randomly assigned to the Baytril® Otic and placebo treatment groups, respectively (approximately a 2:1 active: placebo ratio).

f. Challenge: Natural infection

g. Dosage Form: The formulation used during the clinical trial was identical to the product intended for market.

h. Route of Administration: Ototopical

i. Dose, Frequency and Duration: Investigators were instructed to prescribe a quantity of experimental treatment sufficient to coat the aural lesions. As a general guide, dogs weighing less than 35 lbs. would receive 5-10 drops per treatment while those weighing greater than 35 lbs. would receive 10-15 drops per treatment. Treatments were applied twice daily for a duration of 7-14 days.

j. Treatment Success or Failure: Success/failure was based on clinical response. The otic exams and scoring were repeated on Day 7. If the clinical score for the ears was 2 or less, treatment was stopped. Dogs that showed improvement but not resolution at Day 7 were treated for 7 additional days. The final assessment was performed 3 to 4 days following administration of the last dose. Final scores of 2 or less were considered treatment successes.

4. Microbiology:

During this investigation, 299 microbiological specimens, obtained from 169 cases of unilateral and bilateral otitis externa, were submitted for bacterial and fungal culture. Twenty-four of the samples produced "no growth." The remaining 275 samples yielded 277 bacteria and 149 yeast/fungi for a total of 426 microbial isolates. All bacterial isolates were subsequently subjected to *in vitro* disk diffusion susceptibility testing according to NCCLS-established guidelines. Sensitivity testing was performed for enrofloxacin only.

Table IV.4 Results of Microbial Culture and Susceptibility Testing for Enrofloxacin.

Organism	Total Isolates	% of Total Isolates	Susceptibility (% Susceptible)
Malassezia pachydermatis	126	29.6	N/A
Coagulase positive *Staphylococci* species	115	27.0	114/114 (100%)
Pseudomonas aeruginosa	55	12.9	54/54 (100%)
Enterobacter species	19	4.5	19/19 (100%)
Proteus mirabilis	17	4.0	17/17 (100%)
Streptococci species	16	3.8	0/16 (0%)
Aeromonas hydrophilia	14	3.3	14/14 (100%)
Aspergillus species	13	3.1	N/A
Klebsiella pneumoniae	12	2.8	12/12 (100%)
Candida albicans	10	2.3	N/A
Enterococci species	9	2.1	4/9 (44%)
Escherichia coli	7	1.6	7/7 (100%)
Coagulase negative *Staphylococci* species	5	1.2	5/5 (100%)
Bacillus species	3	0.7	3/3 (100%)
Micrococci species	2	0.47	2/2 (100%)
Acinetobacter anitratus	1	0.23	1/1 (100%)
Serratia marcescens	1	0.23	1/1 (100%)
Staphylococcus epidermidis	1	0.23	1/1 (100%)

5. **Clinical Results:** There was not a direct correlation between the *in vitro* susceptibility testing and the clinical results. Although *Enterococci* species were assessed as "intermediate" responders, 5/5 of the clinical cases in which Enterococci were isolated had successful treatment results. Similarly, treatment for 7/10 cases in which "resistant" *Streptococci* species were cultured was successful. Treatment failed for all cases of *Bacillus* species, *Micrococci* species, *Acinetobacter anitratus*, and *Serratia marcescens*, although these organisms were reported as "susceptible." Successes by treatment site, after 14-days of treatment, are presented in Table IV.5

Table IV.5 Therapeutic Success by Site and Treatment, After 14 Days

Site	Clinical Cure Rate Treated Groups (successes / total ears)	Clinical Cure Rate Placebo Group (successes / total ears)
A	18/24 (75.0%)	0/13
B	12/24 (50.0%)	0/9
C	3/10 (30.0%)	0/2
D	11/26 (42.3%)	6/12 (50.0%)
E	37/43 (86.0%)	3/22 (13.6%)
F	32/37 (86.4%)	0/23
G	9/19 (47.3%)	4/12 (33.3%)
Totals	122/183 (66.7%)**	13/93 (14%)**

**Due to different recruitment rates, total successes, as reported for the active and placebo groups, are not equivalent to the treatment group average.

6. **Adverse Reactions:**

Two of 113 cases (1.8%) treated with Baytril® Otic displayed responses compatible with a local hypersensitivity reaction to one of the components within the formulation. Following 2 –3 days of treatment, aural erythema, swelling, vesicles, pain or pruritis either developed or intensified in these patients. Neither reaction was life threatening and both resolved when treatment was stopped.

7. **Statistical Analysis:**

Therapeutic success occurred in 67 % of aural infections treated with the active formulation and in 14% of aural infections treated with placebo ($\rho = .0143$) after a treatment period of 14 days. The odds for therapeutic success was 14.78 times greater with the active formulation than with the placebo. A mixed model with a logistic link was used to analyze the success variable. The fixed effects were treatment, side (left or right ear), and treatment by side. The random effects were clinic and treatment by clinic. Side and treatment by side were not significant.

8. **Conclusions:**

The data demonstrate that Baytril® Otic, 0.5% enrofloxacin / 1.0% silver sulfadiazine emulsion, is effective for the treatment of otitis externa complicated by the presence of *Malassezia pachydermatis*, coagulase-positive *Staphylococci* species, *Pseudomonas aeruginosa*, *Enterobacter species, Proteus mirabilis*, *Streptococci* species, *Aeromonas hydrophilia*, *Aspergillus* species, *Klebsiella pneumoniae*, and *Candida albicans*.

This conclusion is based on the fact that at least 10 isolates were collected for each of these organisms during the field trial, and ears from which the organisms had been cultured showed clinical cures following treatment with Baytril® Otic for up to 14 days.

Differences between clinical cures and the microbial culture and susceptibility testing results are to be expected because the NCCLS categorical assessments are linked to plasma concentrations of antimicrobial drugs. When a drug is applied topically, the concentration at the site of infection can be higher than that attainable in plasma. Therapeutic failures are also to be expected because factors other than the presence of fungi and bacteria contribute to otitis externa.

V. ANIMAL SAFETY

A. General Safety Study

1. **Type of Study:** Target Species Safety Study

2. **Name and Address of Investigator:**

Elizabeth I. Evans, D.V.M.
Midwest Research Institute
425 Volker Boulevard
Kansas City, MO 64110-2299

3. **General Design:**

a. Purpose: To determine the safety of Baytril® Otic when 10 (1X), 30 (3X), or 50 (5X) drops are administered into the ear canals of dogs twice a day for 42 consecutive days.

b. Test Animals: Twelve male and twelve female beagle dogs, 5.2-13.2 kg in weight, were used in this study. Four males and four females were assigned to each dose group.

c. Control Animals: Four male and four female beagle dogs, 5.9-13.2 kg in weight

d. Ear Condition: Prior to the initiation of treatment, all dogs received a complete aural and otoscopic examination and a hearing evaluation. All dogs had normal ear canals, intact tympanic membranes, and normal hearing.

e. Dosage Form: The study used the final market formulation of Baytril® Otic supplied in 30-mL bottles. Individual syringes were filled with the appropriate amount of test article for each dog. All syringes were masked with tape and the plungers withdrawn to the same level for each syringe, thereby blinding study personnel to the dose group.

The control article was equivalent to the test article in all aspects except for the absence of active ingredients.

f. Route of Administration: Otic topical

g. Dosage Used: 10, 30 or 50 drops of Baytril® Otic were administered in both ears twice a day for 42 consecutive days. This resulted in 1, 3, and 5X the labeled dose given for 3X the labeled duration of treatment.

The control group received 50 drops of vehicle control article in the right ear and no treatment in the left ear.

h. Test Duration: 60 days

i. Parameters measured: The study included clinical observations, measurement of body weight, hematology, clinical chemistry, urinalysis, aural and otoscopic exams, and hearing tests. Hearing was evaluated using a hidden noisemaker to test for responses to sound. Aural erythema and edema were each evaluated using a scale of 0 to 4, with 0 being normal and 4 being severe erythema or edema.

4. Results:

a. Clinical Results: The most notable clinical abnormality was aural erythema. This affected all dogs in the study, and occurred to the same extent in all treatment groups. It began on Day 1 or Day 2, was present in all study dogs by Day 3, and resolved within 2 days after stopping treatment. The erythema was always mild, with scores of 1 or 2 for the duration of the study. Edema was never reported in any dog.

No changes in hearing were reported.

b. Hematology/Clinical Chemistry: No clinically significant changes were reported for hematology or clinical chemistry values.

c. Urinalysis: All urinalysis values were within normal reference ranges.

5. Conclusions:

Twice daily administration of Baytril® Otic at doses up to five times the recommended dose volume and for as long as 42 days produced reversible erythema of the ears. No other adverse effects or signs of toxicity were reported.

B. Oral Safety Study

1. **Type of Study:** This blinded, controlled laboratory study was undertaken to evaluate the local tolerance of healthy canine oral tissues to intentional and repeated misapplications of Baytril® Otic.

2. **Study Director:**

Daniel K. Ciszewski, DVM
Bayer Corporation
Agriculture Division / Animal Health
Shawnee Mission, Kansas

3. **General Design:**

a. Purpose: To determine, by clinical observation, the reactivity of canine oral tissues following intentional and repeated misapplications of Baytril® Otic.

b. Animals: Twelve healthy adult dogs (5 males and 7 females) of assorted breeding, weighing between 8.6 - 20.5 kg. The dogs were free of active gingivitis.

c. Control: Prior to initiation, dogs were randomly assigned to 1 of 2 different treatment groups. Throughout the study, one person intentionally misapplied Baytril® Otic to the dorsum of the tongue and to the left buccal region of Group 1 dogs (n=6). Group 2 dogs (n=6), maintained as controls, were treated similarly but with physiological saline. At predetermined intervals during the study, a second person, blinded to treatment group assignments, carefully inspected the oral cavities of all dogs for the development of adverse, treatment-induced, local reactions.

d. Dosage Form: The test article, a 0.5% enrofloxacin / 1.0% silver sulfadiazine emulsion, was identical to the formulation intended for market.

e. Dose Amount: Each dog was treated with approximately 7 drops of either Baytril® Otic or physiological saline twice daily for 14 consecutive days.

f. Route of Administration: Both the test article and the placebo (saline) were directly applied to the dorsum of the tongue and to the left buccal mucosa.

g. Study Duration: 25 days.

h. Pertinent Measurements/Observations: On study days 0, 4, 8, 15 and 22, a blinded-investigator carefully examined the oral cavities of all study dogs, particularly the lingual and left buccal surfaces, for erythema, edema and other local abnormalities. A numerical scoring system was used to describe and score any identifiable lesions.

4. **Results:** No abnormalities of the oral mucosa were reported in any dogs at any time during this investigation.

5. **Conclusions:** This investigation established the tolerability of healthy canine oral tissues to Baytril® Otic.

VI. HUMAN SAFETY

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. This drug is to be labeled for use in dogs, which are non-food animals. The labeling for this product includes the standard fluoroquinolone caution: "Federal law prohibits the extra-label use of this drug in food-producing animals."

The labeling for this product also contains the following warnings.

Not for human use. Keep out of the reach of children. Avoid contact with eyes. In case of contact, immediately flush eyes with copious amounts of water for 15 minutes. In case of dermal contact, wash skin with soap and water. Consult a physician if irritation develops or persists following ocular or dermal exosures. Individuals with a history of hypersensitivity to quinolone compounds or antibacterials should avoid handling this product. In humans, there is a risk of user photosensitization within a few hours after excessive exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight.

VII. AGENCY CONCLUSIONS

The data submitted in support of this NADA comply with the requirements of section 512 of the Act and section 514.111 of the regulations. The data demonstrate that Baytril® Otic (enrofloxacin and silver sulfadiazine), when used under labeled conditions, is safe and effective for the treatment of otitis externa in dogs.

Under section 512 (c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this product qualifies for THREE years of marketing exclusivity beginning on the date of approval because the application contains substantial evidence of the effectiveness of the drug involved and studies of animal safety required for the approval of the application and conducted or sponsored by the applicant.

This drug product is restricted to use by or on the order of a licensed veterinarian because professional expertise is required to determine the existence of, and microbiological components of, otitis externa. Additionally, veterinary expertise is needed to ensure that the tympanic membrane is intact prior to initial administration of the drug.

VIII. APPROVED PRODUCT LABELING

A. Package Insert

B. 15 mL bottle label

C. 30 mL bottle label

D. Carton for 12 X 15 mL bottles

E. Carton for 6 X 30 mL bottles

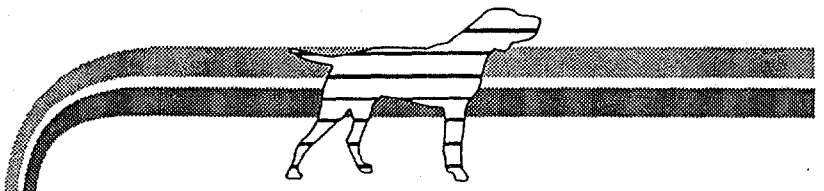
Copies of applicable labels may be obtained by writing to the:

Freedom of Information Office (HFI-35)
FDA
5600 Fishers Lane
Rockville, MD 20857

Baytril® Otic

(enrofloxacin/silver sulfadiazine)

Antibacterial-Antimycotic Emulsion



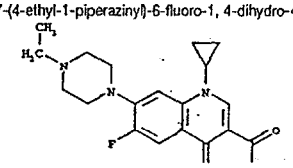
For Ototopical Use In Dogs

Caution: Federal (U.S.A.) Law restricts this drug to use by or on the order of a licensed veterinarian.

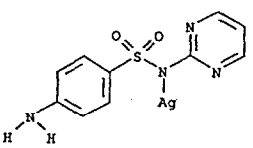
Federal law prohibits the extralabel use of this drug in food-producing animals.

PRODUCT DESCRIPTION:
Each milliliter of Baytril® Otic contains: enrofloxacin 5 mg (0.5% w/v), silver sulfadiazine (SSD) 10 mg (1.0% w/v), benzyl alcohol (as a preservative) and cetylstearyl alcohol (as a stabilizer) in a neutral oil and purified water emulsion. The active ingredients are delivered via a physiological carrier (a nonirritating emulsion).

CHEMICAL NOMENCLATURE AND STRUCTURE:
Enrofloxacin
1-Cyclopropyl-7-(4-ethyl-1-piperazinyl)-6-fluoro-1, 4-dihydro-4-oxo-3-quinolinecarboxylic acid.



Silver Sulfadiazine
Benzenesulfonamide, 4-amino-N-2-pyrimidinyl-monosilver



ACTIONS:
Enrofloxacin, a 4-fluoroquinolone compound, is bactericidal with activity against a broad spectrum of both Gram negative and Gram positive bacteria. Fluoroquinolones elicit their bactericidal activities through interactions with two intracellular enzymes, DNA gyrase (DNA topoisomerase II) and DNA topoisomerase IV, which are essential for bacterial DNA transcription, synthesis and replication. It is believed that fluoroquinolones actively bind with bacterial DNA:ENZYME complexes and thereby inhibit the essential processes catalyzed by the enzymes (DNA supercoiling and chromosomal decatenation).[1] The ultimate outcome of the fluoroquinolone intervention is DNA fragmentation and bacterial cell death.[2,3]

Silver sulfadiazine (SSD) is synthesized from silver nitrate and sodium sulfadiazine.[4] This compound has a wide spectrum of antimicrobial activity against Gram negative and Gram positive bacteria and is also an effective antimycotic.[5,6] SSD suppresses microbial growth through inhibition of DNA replication and modification of the cell membrane.

MICROBIOLOGY:
In clinical field trials, Baytril® Otic demonstrated elimination or reduction of clinical signs associated with otitis externa and *in vitro* activity against cultured organisms. Baytril® Otic is effective when used as a treatment for canine otitis externa associated with one or more of the following organisms: *Malassezia pachydermatis, coagulase-positive Staphylococcus spp., Pseudomonas aeruginosa, Enterobacter spp., Proteus mirabilis, Streptococci spp., Aeromonas hydrophila, Aspergillus spp., Klebsiella pneumoniae,* and *Candida albicans.*

In vitro assays, such as disk-diffusion and agar/broth-dilution, are used to determine the susceptibilities of microbes to antimicrobial therapies. Results of agar/broth-dilution assays are reported as a Minimal Inhibitory Concentration (MIC) which represents the lowest antimicrobial concentration, expressed in µg/mL, capable of inhibiting the growth of a pathogenic microorganism. MICs are used in conjunction with pharmacokinetics to predict the *in vivo* efficacy of systemically administered antimicrobials. Topical administration of Baytril® Otic to an exudate and debris-free canal, however, will generally result in local antimicrobial concentrations that greatly exceed serum and tissue levels resulting from systemic therapy. Therefore, when using Baytril® Otic as a treatment for canine otitis externa, interpret susceptibility data cautiously.

INDICATIONS:
Baytril® Otic is indicated as a treatment for canine otitis externa complicated by bacterial and fungal organisms susceptible to enrofloxacin and/or silver sulfadiazine (see Microbiology section).

EFFECTIVENESS:
Due to its combination of active ingredients, Baytril® Otic provides antimicrobial therapy against bacteria and fungi (which includes yeast) commonly encountered in cases of canine otitis externa.

The effectiveness of Baytril® Otic was evaluated in a controlled, double-blind, multi-site clinical trial. One hundred and sixty-nine dogs (n=169), with naturally occurring active otitis externa participated in the study. The presence of active disease was verified by aural cytology, microbial culture and otoscopy/clinical scoring. Qualified cases were randomly assigned to either Baytril Otic treatment (n=113) or to a comparable placebo-based regimen (n=56). Treatments were administered twice daily for up to 14 days. Assessment of effectiveness was based on continued resolution of clinical signs 3 to 4 days following administration of the last dose.

At study conclusion, Baytril® Otic was found to be a significantly more effective treatment for canine otitis externa than the placebo regimen. Based on the scoring system used to assess treatment response, therapeutic success occurred in 67% of Baytril® Otic-treated infections compared to 14% with placebo (r-value[7] 0.001) after 14 days of treatment.

Bayer

Bayer Corporation, Agriculture Division,
Animal Health, Shawnee Mission, Kansas 66201 U.S.A.

CONTRAINDICATIONS:
Baytril® Otic is contraindicated in dogs with suspected or known hypersensitivity to quinolones and/or sulfonamides.

HUMAN WARNINGS:
Not for human use. Keep out of the reach of children. Avoid contact with eyes. In case of contact, immediately flush eyes with copious amounts of water for 15 minutes. In case of dermal contact, wash skin with soap and water. Consult a physician if irritation develops or persists following ocular or dermal exposures. Individuals with a history of hypersensitivity to quinolone compounds or antibacterials should avoid handling this product. In humans, there is a risk of user photosensitization within a few hours after excessive exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight.

PRECAUTIONS:
The use of Baytril® Otic in dogs with perforated tympanic membranes has not been evaluated. Therefore, the integrity of the tympanic membrane should be evaluated before administering this product. If hearing or vestibular dysfunction is noted during the course of treatment, discontinue use of Baytril® Otic.

Quinolone-class drugs should be used with caution in animals with known or suspected Central Nervous System (CNS) disorders. In such animals, quinolones have, in rare instances, been associated with CNS stimulation which may lead to convulsive seizures.

Quinolone-class drugs have been associated with cartilage erosions in weightbearing joints and other forms of arthropathy in immature animals of various species.

The safe use of Baytril® Otic in dogs used for breeding purposes, during pregnancy, or in lactating bitches, has not been evaluated.

ADVERSE REACTIONS:
During clinical trials, 2 of 113 (1.7%) dogs exhibited reactions that may have resulted from treatment with Baytril® Otic. Both cases displayed local hypersensitivity responses of the aural epithelium to some component within the Baytril® Otic formulation. The reactions were characterized by acute inflammation of the ear canal and pinna.

To report a suspected adverse reaction call 1-800-633-3796.

SAFETY:
General Safety Study:
In a target animal safety study, Baytril® Otic was administered in both ears of 24 clinically normal beagle dogs at either recommended or exaggerated dosages: 10, 30 or 50 drops applied twice daily for 42 consecutive days. A control group of 8 beagle dogs was treated by administering 50 drops of vehicle in one ear twice daily for 42 consecutive days, with the contralateral ear untreated. Erythema was noted in all groups, including both treated and untreated ears in the controls, which resolved following termination of treatment.

Oral Safety Study:
In order to test safety in case of ingestion, Baytril® Otic was administered, twice daily for 14 consecutive days, to the dorsum of the tongue and to the left buccal mucosa of 6 clinically normal dogs. No adverse local or systemic reactions were reported.

DOSAGE AND ADMINISTRATION:
Shake well before each use.

Tilt head so that the affected ear is presented in an upward orientation. Administer a sufficient quantity of Baytril® Otic to coat the aural lesions and the external auditory canal. As a general guide, administer 5-10 drops per treatment in dogs weighing 35 lbs. or less and 10-15 drops per treatment in dogs weighing more than 35 lbs. Following treatment, gently massage the ear so as to ensure complete and uniform distribution of the medication throughout the external ear canal. Apply twice daily for a duration of up to 14 days.

STORAGE:
Store between 4 and 25°C (40 - 77°F). Store in an upright position. Do not store in direct sunlight.

HOW SUPPLIED:
Baytril® Otic (enrofloxacin/silver sulfadiazine)

Code Number	Size	Presentation
0420	15 mL	Oval plastic bottle with dropper tip and extended tip closure
0421	30 mL	Oval plastic bottle with dropper tip and extended tip closure

REFERENCES:
1. Hooper DC and Wolfson JS. Mechanisms of quinolone action and bacterial killing, in Quinolone Antimicrobial Agents. Washington DC, American Society for Microbiology, 2nd ed., 1993, 53-75.
2. Gootz TD and Brightly KE. Fluoroquinolone antibacterial: mechanism of action, resistance and clinical aspects. Medicinal Research Reviews 1996; 16 (5): 433-486.
3. Drlica K and Zhoa X. DNA gyrase, topoisomerase IV and the 4-quinolones. Microbiology and Molecular Biology Reviews 1997; 61(3): 377-392.
4. Fox CL. Silver sulfadiazine: a new topical therapy for *Pseudomonas* in burns. Archives of Surgery 1968; 96:184-188.
5. Wlodkowski TJ and Rosenkranz HS. Antifungal activity of silver sulfadiazine. Lancet 1973; 2:739-740.
6. Schmidt A. *In vitro* activity of climbazole, clotrimazole and silver sulfadiazine against isolates of *Malassezia pachydermatis*. J of Vet Medicine Series B 1997; 44: 193-197.

For a copy of the Material Safety Data Sheet (MSDS) or to report Adverse Reactions call Bayer Customer Service at 1-800-633-3796.

Bayer

Bayer Corporation,
Agriculture Division, Animal Health,
Shawnee Mission, Kansas
66201 U.S.A.

U.S. Patent No: 5,753,269

80004200 R.0
August, 2000

NADA # 141-176, Approved by FDA

Baytril® Otic

(enrofloxacin/silver sulfadiazine)

Antibacterial-Antimycotic Emulsion

For Ototopical Use In Dogs

CAUTION: Federal (U.S.A.) law prohibits the extra-label use of this drug in food-producing animals.

12 bottles of 15 mL each

Bayer

Bayer Corporation, Agriculture Division, Animal Health, Shawnee Mission, Kansas 66201 U.S.A.
NADA 141-176, Approved by FDA

AB01

77004200, R.0

WARNINGS: Not for human use. Keep out of the reach of children.

STORAGE: Store between 4 and 25°C (40 – 77°F). Store in an upright position. Do not store in direct sunlight.

For a copy of the Material Safety Data Sheet (MSDS) or to report Adverse Reactions call Bayer Customer Service at 1-800-633-3796

Read package insert carefully for complete details.

0420

7 24089 90420 1

Baytril® Otic

(enrofloxacin/silver sulfadiazine)

Antibacterial-Antimycotic Emulsion

™

For Ototopical Use In Dogs

Caution: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

Federal law prohibits the extralabel use of this drug in food-producing animals.

12 bottles of 15 mL each

Bayer

Bayer Corporation, Agriculture Division, Animal Health, Shawnee Mission, Kansas 66201 U.S.A.
NADA 141-176, Approved by FDA

Baytril® Otic is indicated as a treatment for canine otitis externa complicated by bacterial and fungal organisms susceptible to enrofloxacin and/or silver sulfadiazine.

CONTAINS PER mL: enrofloxacin 5 mg (0.5% w/v), silver sulfadiazine (SSD) 10 mg (1.0% w/v), benzyl alcohol (as a preservative) and cetylstearyl alcohol (as a stabilizer) in a neutral oil and purified water emulsion.

Read package insert carefully for complete details.

MAGENTA CYAN BLACK

Baytril® Otic

(enrofloxacin/silver sulfadiazine)

Antibacterial-Antimycotic Emulsion

For Ototopical Use In Dogs

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

Federal law prohibits the extralabel use of this drug in food-producing animals.

6 bottles of 30 mL each

Bayer

Bayer Corporation, Agriculture Division, Animal Health, Shawnee Mission, Kansas 66201 U.S.A.

NADA 141-176, Approved by FDA

ABO4

Baytril® Otic

(enrofloxacin/silver sulfadiazine)

Antibacterial-Antimycotic Emulsion

For Ototopical Use In Dogs

6 bottles of 30mL each

770042 10,R.0

WARNINGS: Not for human use. Keep out of the reach of children.

STORAGE: Store between 4 and 25°C (40–77°F). Store in an upright position. Do not store in direct sunlight.

For a copy of the Material Safety Data Sheet (MSDS) or to report Adverse Reactions call Bayer Customer Service at 1-800-633-3796

Read package insert carefully for complete details.

0421

7 24089 90421 8

Baytril® Otic

(enrofloxacin/silver sulfadiazine)

Antibacterial-Antimycotic Emulsion

™

For Ototopical Use In Dogs

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Federal law prohibits the extralabel use of this drug in food-producing animals.

6 bottles of 30 mL each

Bayer

Bayer Corporation, Agriculture Division, Animal Health, Shawnee Mission, Kansas 66201 U.S.A.
NADA 141-176, Approved by FDA

Baytril® Otic is indicated as a treatment for canine otitis externa complicated by bacterial and fungal organisims susceptible to enrofloxacin and/or silver sulfadiazine.

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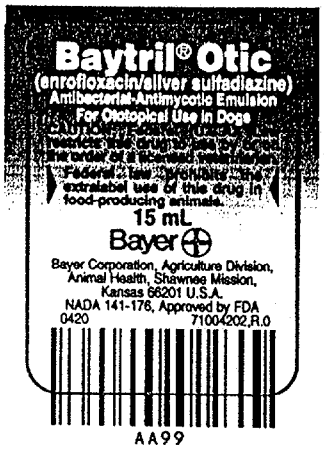
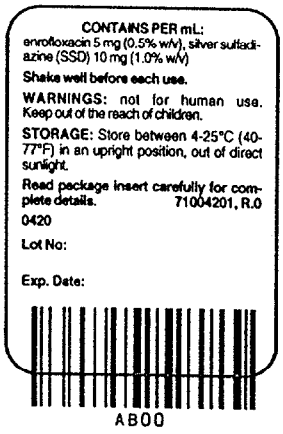
Read package insert carefully for complete details.

MAGENTA CYAN BLACK





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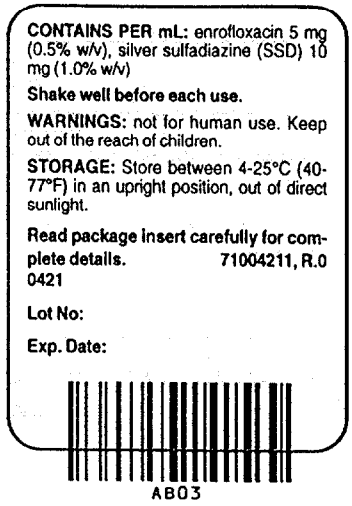
Enlarged



Color: PMS 247 Black

Label: 1.656" H x 1.25" W

Line Screen 133

Barcode: 128 @ 80%

Enlarged